PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 218-TAM-2004	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IN2005/000055	International filing date *(day/month/year)* 22.02.2005	Priority date *(day/month/year)* 23.02.2004
International Patent Classification (IPC) or national classification and IPC C07C303/42, C07C311/37, C07B57/00		
Applicant CADILA HEALTHCARE LIMITED		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 19.09.2005	Date of completion of this report 15.02.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer English, R Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2005/000055

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-9 as originally filed

   Claims, Numbers

   1-25 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2005/000055

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: EP 0 257 787 A (Yamanouchi Pharmaceutical) 2 March 1988
D2: CA 1 282 077 C (Yamanouchi Pharmaceutical) 26 March 1991

1. **Subject-matter**

The present application concerns a process for the manufacture of (R)- or (S)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide by resolving racemic 5-(2-amino-propyl)-2-methoxybenzenesulphonamide in four steps using (D)- or (L)-tartaric acid. In particular, in the examples the tartrate salt is prepared by reaction of the racemic amine with optically active tartaric acid in a mixture of methanol and water or dimethylformamide; filtered off; treated twice at reflux in a mixture of methanol and water and then the optically active free amine with an enantiomeric excess of greater than 99% is liberated by treatment with aqueous sodium hydroxide.

Present claim 1 is not clear in that in step (c) it contains the expression "a solvent system of the kind such as hereinbefore described". It is not apparent which solvents this could include other than the methanol/water mixtures in examples 4,5 and the alcohol/water mixtures disclosed in claim 14. In any case, claims may not rely on references to the description except where absolutely necessary (Rule 6.2(a) PCT).

2. **Novelty**

Documents D1 (pages 10-14) and D2 (examples 1-3) describe the synthesis of (R)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide. Neither of these processes involves the resolution of racemic 5-(2-aminopropyl)-2-methoxybenzenesulphon-amide. Consequently, the subject-matter of claims 1-25 appears to be novel and to satisfy the requirements of Article 33(2) PCT.

3. **Inventive step**

The present application does not meet the criteria of Article 33(1) PCT, because the

subject-matter of claims 1-25 does not involve and inventive step in the sense of Article 33(3) PCT.

Document D1, which is considered to represent the most relevant state of the art of claim 1, discloses (examples 1-3) a three-step process for the preparation of (R)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide starting from the achiral 2-methoxy-5-(2-oxopropyl)benzenesulfonamide in an overall yield of around 40%. In this prior-art process the chirality is introduced into the molecule at an early stage and no resolution step is required. No technical effect is apparent which results from preparing the racemic amine and then resolving it as the last step.

The problem to be solved by the present application may therefore be regarded as the provision of an alternative process for the manufacture of optically pure 5-(2-aminopropyl)-2-methoxybenzenesulphonamide. The applicant solves this problem by means of the resolution process of present claim 1.

The use of (D)- or (L)-tartaric acid in the resolution of amines via their diastereomeric salts is well-known in the art, so the skilled person would set out to employ this acid in the resolution of racemic 5-(2-aminopropyl)-2-methoxybenzenesulphonamide without the exercise of inventive skill, in order to solve the problem posed, since he would expect it to succeed.

The technique of kinetic resolution of diastereomeric salts is also well-known in the art. The choice of this technique and selecting suitable solvents and other conditions are considered routine operations which the skilled person would employ without the exercise of inventive skill, in order to solve the problem posed.

Furthermore, is noted that in the first treatment (example 4) between 30 and 45 % of the diastereomeric salt is lost, whilst in the second (example 5) between 24 and 27 % is lost. Without knowing the nature (i.e. the optical purity) of the material left behind in the methanol/water filtrate, the improvement in optical purity may be inferred merely to be the result of an unsurprising purification effect of the heat treatment in step (c) and not the process of kinetic resolution. Indeed the applicant refers to the process of step (c) as a purification or the product of this step as the purified salt (see

for example page 2, lines 23-33; page 7, lines 1-2; page 8, lines 8-9; claim 23).

Dependent claims 2-25 do not appear to contain any features which, in combination with the features of any claim to which they refer, can be acknowledged as involving inventive activity.